

Toward a Practical Impedimetric Biosensor: A Micro-Gap Parallel Plate Electrode Structure That Suppresses Unexpected Device-to-Device Variations

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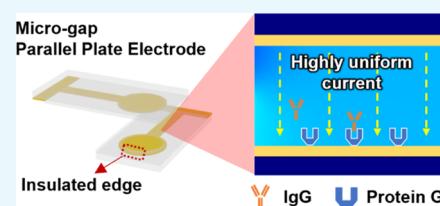


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Supporting Information

ABSTRACT: We propose a rational electrode design concept for affinity biosensors based on electrochemical impedance spectroscopy to substantially suppress unexpected device-to-device variations. On the basis that the uniformity of the current distribution affects the variation, a novel micro-gap parallel plate electrode (PPE) was developed, where two planar electrodes with edges covered with a SiO₂ layer were placed face to face. The structure provides a uniform current distribution over the planar electrode surface and maximizes the contribution of the planar electrode surface to sensing. For a comparative study, we also fabricated a micro-structured interdigitated electrode (IDE) that has been widely adopted for high-sensitivity measurement, although its current is highly concentrated on the electrode edge corner. Protein G (PrG) molecules were immobilized on both electrodes to prepare an immunoglobulin G (IgG) biosensor on which the specific binding of PrG–IgG can occur. We demonstrated that the IgG sensor with the PPE has small device-to-device variations, in strong contrast to the sensor with the IDE having large device-to-device variations. The results indicate that the current distribution on the electrode surface is important to fabricating electrochemical impedance spectroscopy biosensors with small device-to-device variations. Furthermore, it was found that the PPE allows ultrasensitive detection, that is, the sensor exhibited a linear range from 1×10^{-13} to 1×10^{-7} mol/L with a detection limit of 1×10^{-14} mol/L, which is a record sensitivity at low concentrations for EIS-based IgG sensors.



INTRODUCTION

Biosensing technology currently attracts much research interest in a wide variety of fields, such as clinical analysis (e.g., the analysis of biomarkers and hormones), food safety control, and environmental monitoring.^{1–3} There is an increasing need for an analytical technique that allows signal amplification and noise reduction and thus realizes low detection limits for a wide range of target analytes depending on the field.^{4,5} The enzyme-linked immunosorbent assay has generally been shown to be suitable in such a scenario and has been well developed for diagnosis and laboratory examinations.^{6–8} However, the technique suffers from several drawbacks, such as the time and effort required, the requirement for high operational skill, and the need for sophisticated instrumentation. Electrochemical impedance spectroscopy (EIS) has the advantages of a rapid and simple pretreatment, minimal manipulation, and uncomplicated instrumentation. EIS, which is an electrochemical technique, works by measuring the impedance change induced by a specific binding event of receptors immobilized on a surface through the relationship between applying a small sinusoidal perturbation potential and the derived current response.^{9–14} In recent decades, many efforts have been made to optimize the electrode structure for EIS measurements.^{15,16} In particular, the electrode design of an interdigitated microelectrode (IDE) array has been widely adopted. This structure comprises a series of parallel microband electrodes in

which alternating microbands are connected and form a pair of interdigitated electrode fingers. The small gap between the cathodic and anodic electrodes results in the IDE having a high collection efficiency owing to the enhanced redox cycling between the electrodes, providing an advantage in the detection of a small amount of analyte.^{17,18} In addition, the need for a reference electrode can be eliminated in an equimolar environment such that $[\text{Fe}(\text{CN})_6]^{3-}$ and $[\text{Fe}(\text{CN})_6]^{4-}$ exist at the same molar concentration, which makes EIS easy and simple to carry out with the two-electrode system rather than the conventionally used three-electrode system.^{18,19} We have been developing several biosensors based on the IDE structure and demonstrated their highly sensitive and selective responses to target analytes.^{20–25} In the cited studies, we noted that a major drawback of an IDE-based affinity sensor is its low reproducibility, although the structure greatly improves the sensitivity. It has been frequently observed that individual IDE biosensors have different profiles for the calibration curves (sensing signal vs concentration) of

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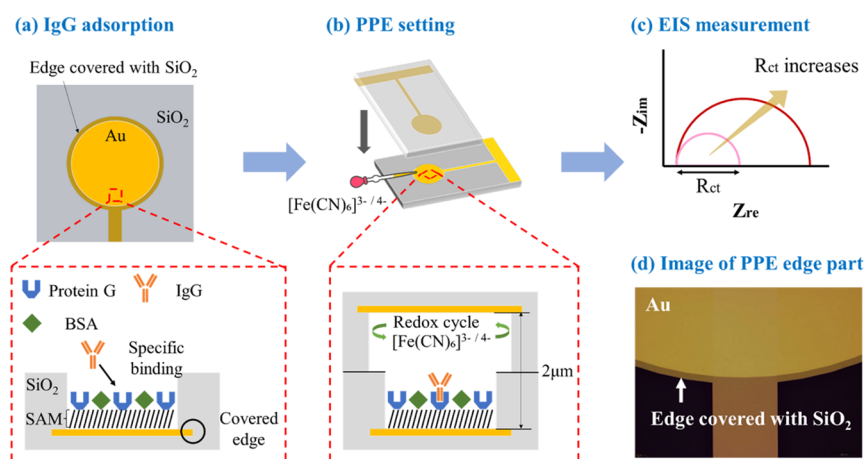


Figure 1. Schematic of the experiment conducted to characterize the IgG sensor performance. (a) Top view of the working electrode (upper) and specific binding of IgG with PrG (lower). (b) Setting configuration of the PPE (upper) and schematic of the $[\text{Fe}(\text{CN})_6]^{3-/4-}$ redox cycle for EIS measurement (lower). (c) R_{ct} evaluation with Nyquist plot. (d) Magnified image of the PPE edge part.

individual chips even when they are from the same batch of IDE fabrication. Such a low reproducibility of the individual chips presents a serious obstacle to sensor application because a prior calibration procedure is required for each chip. A similar poor reproduction of the IDE has been reported in other studies,^{26,27} but its origin and solution remain open questions. It is thus an important issue for the design of a practical EIS biosensor to establish a novel electrode design structure that avoids this problem. We suppose that a high current density at the edge corner of the electrode is the most likely origin of the low reproducibility of an IDE. Several studies conducting finite element analysis showed that the electric flux between the adjacent electrodes of the IDE is highly concentrated on the edge corner of the electrodes.^{28–32} However, the edge part can be easily damaged in the lithography processes involving lift-off and chemical etching applied to the pattern IDE shape on a substrate. EIS measures the rate of charge transfer between the solution and the electrode that the electric current passes through and, therefore, EIS with IDE simply measures the rate of charge transfer on the disordered surface. We suppose that such a current focusing on the edge corner explains the low reproducibility of IDE-based EIS sensors.

One way to overcome the above drawback is to configure a new electrode structure that has an insulated electrode edge and enables the current to be uniformly distributed on a planar electrode surface. The simplest electrode design that provides the above characteristics is the parallel plate electrode (PPE) structure, where two electrode plates are placed face-to-face with a narrow gap. The electric current flows along the shortest path between the electrodes, and the electric flux is thus distributed uniformly on the planar surface. This is close to the ideal surface condition for EIS measurement. For this design, the gap between the two electrodes can be precisely controlled by varying the thickness of the insertion layer.

In this report, we demonstrate that the PPE structure offers greater reproducibility in EIS measurement than the IDE structure. We first simulate the current density for both the PPE and IDE to visualize current distributions depending on the electrode design. We then compare the EIS biosensor performance for the PPE and IDE, using the specific binding of immunoglobulin G (IgG) with protein G (PrG) as a test reaction,^{33–37} on the basis of Nyquist plots and calibration

curves (Figure 1). We finally confirm that a non-specific binding event has no effect on the sensor response. The obtained results indicate that the PPE has a great advantage in terms of the reproducibility of EIS measurements as well as the ultrasensitive detection of IgG.

RESULTS AND DISCUSSION

Simulation of the Current Density. The current density was simulated using COMSOL Multiphysics ver. 5.3 (COMSOL AB, Sweden), which adopts finite element analysis. In the simulation, the gap between the electrodes was set at a constant distance of 2 μm for both the IDE (10 μm band width) and PPE (3 mm working electrode and 5 mm counter electrode) models with a 10 mV voltage applied to the deionized water ($\sigma = 5.5 \times 10^{-6}$ S/m). The electrodes in the models consist of a 200 nm thickness Au layer deposited on a SiO₂ substrate ($\sigma = 1 \times 10^{-14}$ S/m, $\epsilon_r = 4.2$). The simulations were performed assuming that the parameters of electrical conductivity and dielectric constant are isotropic. Figure 2a

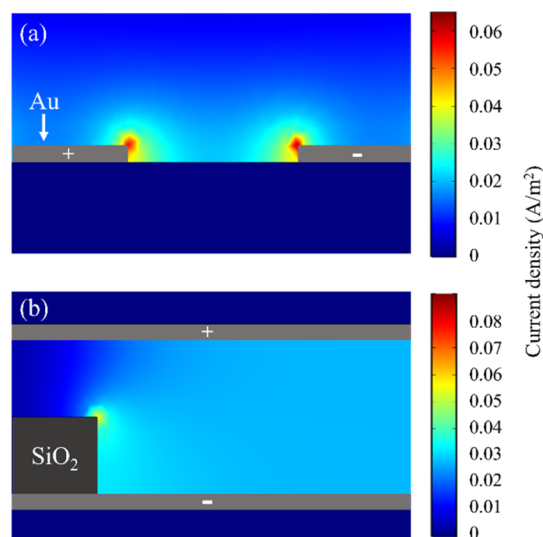


Figure 2. Simulated distribution of the current density around the electrodes of an IDE (a) and PPE (b). Geometric parameters of both electrodes were a thickness of 200 nm and a gap of 2 μm . The PPE edge was covered with a 1 μm -thick SiO₂ layer.

shows the current density around a finger of the IDE. It is seen that the electric current is highly concentrated on the edge corner of the IDE and thinly distributed on the flat surface. Such a highly inhomogeneous distribution of the current is due to the closely spaced side-by-side electrode arrangement. Generally, the surface portion gathering a higher flux of current more strongly affects the EIS measurement. Accordingly, the EIS measurement with the IDE substrate reflects mainly the surface condition of the edge corner. However, the surface condition of the edge corner is considerably disordered or inhomogeneous because the edge is initially damaged in the etching process. In this sense, the EIS measurements with IDE substrates readily suffer from instability or low reproducibility. Figure 2b shows the current density around the PPE. In contrast with the current distribution on the IDE, the current distribution on the PPE is extremely uniform without there being any area of high or low current density on the electrode surface. A major reason for such a uniform distribution is that the two electrode plates are closely placed in a face-to-face geometry and, accordingly, the current flows directly along the shortest normal direction between the electrodes over the surface. Such a uniform current distribution on the flat surface is advantageous for obtaining stable EIS results because the surface has the most smooth and well-ordered structure on the electrode outside. The EIS measurement using the uniformly distributed current on the ideal condition surface should be highly reproducible.

Characterization of the IgG Sensor. The results of EIS measurements made with the PPE are shown as Nyquist plots (Z_{im} vs $-Z_{re}$) in Figure 3a. These results were obtained for

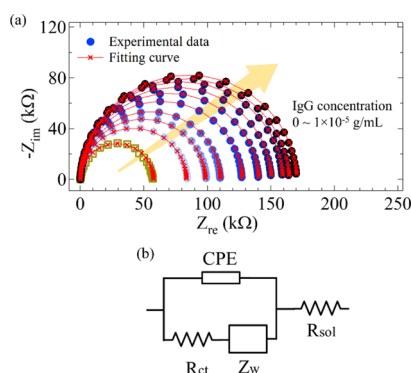


Figure 3. (a) Nyquist plots of the EIS spectra obtained using a PrG-modified PPE at various concentrations of IgG. The solid lines represent the fitting curves. (b) Equivalent circuit for data fitting.

successive immersion and measurement cycles at IgG concentrations ranging from 0 to 10^{-5} g/mL. The figure shows that a semicircular profile was obtained for each measurement. The diameter of the semicircle increased with the IgG concentration. The diameter of the semicircle represents the charge-transfer resistance (R_{ct}), which is generally used as the sensor signal for a Faradic EIS biosensor. During each incubation of the sample in the IgG solution, there were specific binding events between IgG and PrG on the electrode surface. In the EIS measurements of the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ redox probe solution, this binding of IgG prevents reversible electron transfer between the electrode and redox probe and thus increases R_{ct} . Accordingly, the observed gradual increase in the diameter of the semicircle as a function of the IgG concentration reflects the IgG binding

event on the electrode surface. Reliable R_{ct} values were obtained by fitting the impedance spectra to the Randles equivalent circuit model (Figure 3b).³⁸ In this modeling, the electrode–electrolyte interface is modeled as a parallel circuit of R_{ct} and a constant phase element (CPE). The CPE expresses the frequency dependence of the double-layer capacitance (C_{dl}) arising from the capacitance dispersion. R_{ct} is the main signal of the EIS measurement and indicates the degree of IgG binding on the electrode surface as described above. In the low-frequency range, the diffusion from the redox probe to the electrode can be slower than the charge transfer, and accordingly, the Warburg impedance (Z_w) must be introduced in series with R_{ct} to represent this behavior. R_{sol} is the resistance of the solution between the two electrodes. All these parameters were fit to each impedance spectrum and their values determined. The solid lines in Figure 3a are obtained from the best-fitting parameters and well reproduce all the experimental results, indicating that the obtained parameter sets well explain the interfacial behavior. The details of the fitting results are given in the Supporting Information (Figure S1 and Table S1).

The IgG sensor was quantitatively assessed by the dependence of $R_{ct}/R_{ct}(0 \text{ g/mL})$ on the IgG concentration, where $R_{ct}(0 \text{ g/mL})$ is R_{ct} for no IgG. Figure 4 shows the calibration curves of $R_{ct}/$

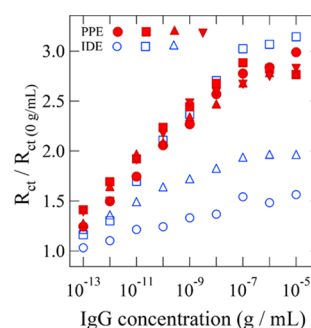


Figure 4. Calibration curves for four individual PPE sensors (red filled symbols) and three individual IDE sensors (blue open symbols).

$R_{ct}(0 \text{ g/mL})$ versus the logarithmic IgG concentration obtained from several samples of each electrode type. All the profiles show a linear increase of $R_{ct}/R_{ct}(0 \text{ g/mL})$ in the IgG concentration range from 1×10^{-13} to 1×10^{-7} g/mL, which corresponds to IgG–PrG-specific binding on the electrode surface depending on the concentration. The lowest detectable concentration was 1×10^{-14} g/mL (see Supporting Information, Figure S2). Above this range, $R_{ct}/R_{ct}(0 \text{ g/mL})$ remains at a constant value because the PrG binding sites on the electrode surface are saturated with IgG. Such behaviors are commonly observed for EIS-based biosensors. Figure 4 shows that the sensor with the PPE has better reproducibility than that with the IDE; that is, the four PPE samples have similar calibration curves, whereas the three IDE samples have different profiles. As described in the previous section, we suppose that this difference in reproducibility of the calibration curve stems from the current distribution and surface condition of the electrode. The uniform current distribution on the well-ordered surface of the PPE provides constant calibration curves, whereas the highly concentrated current on the disordered edge corner of the IDE can cause unstable profiles.³⁹ The results clearly demonstrate that the PPE is more favorable in sensor applications than the IDE.

Selectivity of the IgG Sensor. We performed two experiments to assess the IgG selectivity of our biosensor using the PPE. We first investigated the interfering effect of IgA on the EIS measurement. IgA is the second-largest component of human immunoglobulin and has a protein structure similar to that of IgG. A series of EIS measurements were performed over the IgA concentration range of 1×10^{-13} to 1×10^{-5} g/mL, from the lowest to the highest concentration, with the same experimental conditions as for IgG. Figure 5a shows the obtained result together with the

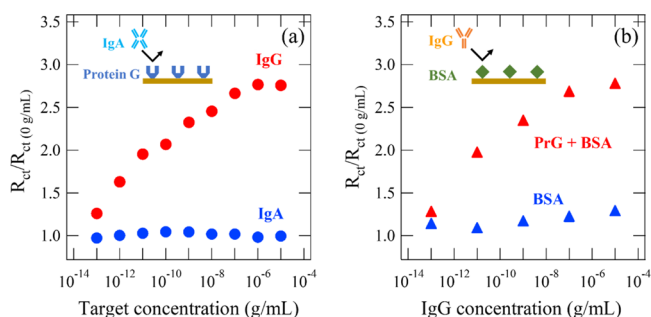


Figure 5. (a) Selectivity of the PPE sensor. Calibration curves obtained for IgG exposure (red circles) and IgA exposure (blue circles) are plotted. (b) Confirmation of non-specific binding. Calibration curves obtained for PPEs with (red triangle) and without (blue triangle) PrG immobilization are plotted.

previous result for IgG. We see that R_{ct} was almost independent of the concentration for IgA in contrast with that for IgG, which indicates that our IgG sensor does not respond to IgA at all.

We then prepared a blank surface through the immobilization of only bovine serum albumin (BSA). On this surface, there was no PrG receptor, and IgG only attached through non-specific binding (*i.e.*, physical adsorption). We made the same series of IgG sensing performance measurements for the sample and obtained a calibration curve, which is shown in Figure 5b together with the previous result obtained with the PrG immobilized. It is seen that R_{ct} remains at an almost constant low value even for solutions with a higher IgG concentration. We conclude from this result that non-specific binding is avoidable by passivating the surface with BSA.

Finally, the analytical performances of the PPE-based IgG sensor with those previously reported have been compared (Table 1). The data comparison shows that the PPE sensor is more sensitive than the other sensors reported. In particular, the linear range of the PPE sensor extends to 2 orders of magnitude lower concentrations than the other sensors, which is a record sensitivity at low concentrations for an EIS-based

IgG sensor. These research results indicate that PPE-based EIS sensors have highly reproducible and ultrasensitive characteristics.^{40–44}

CONCLUSIONS

Progressing toward a practical impedimetric biosensor, we developed a novel micro-gap PPE that has not only higher reproducibility than the traditional interdigitated electrode but also ultrasensitive characteristics. An important aspect of obtaining high reproducibility in our study was to cover the edge of the electrode with an insulator so that it does not contribute to the sensing. As a future perspective on the present work, we suppose that our novel PPE is suitable for a sensor array system because unexpected inherent sensor variability during the manufacturing process should be reduced for a sensor array system.^{45,46} The results of the study are useful for the further development of highly reproducible biosensors.

METHODS

The sequence of the experiment is shown in Figure 1. A set of PPEs comprises two pieces of Au-patterned quartz glass (see Figure 1). The substrate was prepared adopting standard photolithography techniques. We fabricated two types of electrode with different diameters: a working electrode (3 mm) on which an IgG receptor PrG was immobilized and a counter electrode (5 mm) of a pure Au surface. On each electrode, a SiO_2 layer with a thickness of 1 μm was formed around the patterned electrode through plasma-enhanced chemical vapor deposition. An important aspect of this process is that the edge corner of the electrode was covered with the SiO_2 layer because the insulator covering the edge corner gives rise to a uniformly distributed current flux on the electrode. The PPE structure was then created by dropping a solution onto the working electrode plate and covering the solution with the counter electrode plate. For comparison, we fabricated IDE chips using similar photolithography techniques. The fabrication details are described in the Supporting Information (Figure S3).

The working electrode surface was modified with a self-assembled monolayer of a mixed molecular system (11-mercaptopundecanoic acid:6-mercapto-1-hexanol ratio of 1:3). PrG was covalently attached to the self-assembled monolayer. The residual active esters were blocked with BSA. The conditions of the surface modification are detailed in the Supporting Information (Figure S4).

The experimental procedure adopted to characterize the IgG sensor performance is shown in Figure 1b. First, the PrG-functionalized working electrode of the PPE was immersed in IgG having a fixed concentration for 20 min at 20 $^\circ\text{C}$ and then rinsed with distilled water and dried under a N_2 flow. A phosphate buffered saline (PBS) solution containing an equimolar mixture (5 mM) of $[\text{Fe}(\text{CN})_6]^{3-}$ and $[\text{Fe}(\text{CN})_6]^{4-}$ was dropped on the working electrode, and the counter electrode was then placed to cover the drop, resulting in the thin liquid PBS layer (having a thickness of 2 μm) being sandwiched between the two electrodes. EIS measurements were carried out using this two-electrode system at an equilibrium potential of the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ couple of 10 mV in the frequency range of 0.1– 1×10^5 kHz. The apparatus used for the measurements was an Autolab PGSTAT128N (Metrohm, The Netherlands).

Table 1. Comparison of Different Immunosensors for the Determination of IgG

method	linear range (g/mL)	LoD (g/mL)	ref.
EIS	1.13×10^{-8} – 1.13×10^{-4}		40
EIS	5×10^{-10} – 2×10^{-7}	3×10^{-11}	41
EIS	5×10^{-10} – 1.25×10^{-7}	2×10^{-11}	42
DPV ^a	1×10^{-10} – 5×10^{-8}	2×10^{-11}	43
DPV ^a	1.2×10^{-11} – 3.52×10^{-7}	6×10^{-12}	44
EIS	1×10^{-13} – 1×10^{-7}	1×10^{-14}	this work

^aDifferential pulse voltammetry.

It is worth noting that the PPE fabricated in this study can be applied to two-electrode cyclic voltammetry (CV) measurements in the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ equilibrium condition. We observed that the current in the CV measurements with PPE was significantly increased with a smaller electrode gap distance (Figure S5). This result indicates that the $[\text{Fe}(\text{CN})_6]^{3-}/^{4-}$ redox cycle is enhanced between a narrow PPE gap.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c06942>.

Numerical fitting parameters, lowest detection limit, PPE fabrication process, electrode functionalization process, and CV measurement with PPE (PDF)

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Notes

The authors declare no competing financial interest.

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